LORATADINE TRANSDERMAL DEVICE AND METHODS

This application claims the benefit of U.S. Provisional Application No. 60/242,514, filed October 23, 2001, hereby incorporated by reference.

Background of the Invention

It is the intent of all sustained-release pharmaceutical preparations to provide a longer period of pharmacologic effect after the administration of a drug than is ordinarily experienced after the administration of immediate release preparations of the same drug. Such longer periods of efficacy can provide many inherent therapeutic benefits that are not achieved with corresponding immediate release preparations. The benefits of prolonged treatment of the nasal and non-nasal symptoms of seasonal allergic rhinitis or chronic idiopathic urticaria afforded by sustained release oral preparations have become universally recognized and oral sustained-release preparations are commercially available.

Another approach to sustained delivery of a therapeutically active agent is transdermal delivery systems, such as transdermal patches. Generally, transdermal patches contain a therapeutically active agent, a reservoir or matrix containing the active ingredient(s) and an adhesive which allows the transdermal device to adhere to the skin, allowing for the passage of the active agent from the device through the skin of the patient. Once the active agent has penetrated the skin layer, the drug is absorbed into the blood stream where it can exert a desired pharmacotherapeutic effect.

In spite of the known art related to transdermal therapy, there exists a need for the transdermal delivery of a beneficial agent for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria.

Loratadine, commercially available as Claritin® in the U.S. from Schering Corporation (Kenilworth, NJ 07033, U.S.A.), is a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity, with the chemical name, ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate, and it is used mainly for treating nasal and non-nasal symptoms of seasonal allergic rhinitis, but may also be used in the treatment of chronic idiopathic urticaria, a common skin disorder . It is in the form of a white to off white powder, not soluble in water, but very soluble in organic solvents. Loratadine inhibits the activity of the substance,

histamine, thus r[illegible]ng the allergic effects caused by [illegible] substance such as itching, sneezing, runny nose and watery eyes. Loratadine is preferable to other antihistamines because it is nonsedating and does not cause cardiac arrhythmias brought on by use of some other antihistamines. The recommended oral dosage of loratadine for adults and children 12 years old or older is 10 mg once daily. In patients with liver or renal problems, the initial oral dosage of loratadine should be 10 mg every other day.

Seasonal allergic rhinitis (hay fever) is a term used to describe the symptoms caused seasonally by an allergic reaction that occurs in the eyes, nose, and throat in response to airborne allergens such as pollen from trees, grasses, and weeds. Other possible allergens include dust mites, molds, and animal dander. The allergens produce an allergic response by misleading the immune into thinking that the allergen is a harmful substance, thereby causing the immune system to produce antibodies to this specific allergen. When that allergen enters the immune system again, a reaction occurs between the allergen and IgE antibodies triggering the release of substances such as histamine from mast cells and other cells, producing symptoms such as runny nose, watery eyes, sneezing, and itching.

Chronic urticaria is an allergic skin disorder characterized by hives, e.g. red welts or small bumps, on the skin which are very itchy. Patients with chronic urticaria have hives that last longer than six months. This skin disorder is caused by an antigen-antibody reaction in which histamine and other substances such as acetyl choline are released from mast cells and other cells causing symptoms such as swelling, itching, pain, and rash. There are also cases in which there are no known causes for the hives (chronic idiopathic urticaria). As with chronic urticaria, antihistamines are used for treating chronic idiopathic urticaria.

Symptoms of seasonal allergic rhinitis and chronic idiopathic urticaria are improved by treatment with nonsedating antihistamines. Nonsedating antihistamines such as loratadine (The Merck Index, 11th Edition, Merck & Co., Inc., Rahway, N.J. U.S.A. 1989, hereby incorporated by reference) act as an antagonist to the peripheral histamine H_1 receptor by selectively binding to this receptor, thereby blocking histamine from being released from the immune system and thus preventing histamines unwanted effects. (Goodman and Gillmans, The Pharmacological Basis of Therapeutics, 9th Edition, hereby incorporated by reference).

Following oral administration, loratadine is rapidly absorbed, fast acting, and undergoes extensive first pass metabolism to the active metabolite descarboethoxyloratadine.

Food delays absorption, so loratadine should be taken on an empty stomach. Pharmacokinetic studies have revealed that the onset of antihistamine activity occurs within 1-3 hours following administration of loratadine, reaching a maximum at 8-12 hours and lasting in excess of 24 hours. There was no evidence of tolerance to this effect after 28 days of dosing with loratadine. After 10 days of dosing, a mean peak plasma concentration of 1.3 hours and 2.3 hours (T_{max}) was observed in loratadine and the active metabolite, respectively. The mean elimination half-life observed in normal adults was 8.4 hours for loratadine and 28 hours for active metabolite. In patients with chronic liver disease, a mean half-life for loratadine and descarboethoxyloratadine of 24 hours and 37 hours were observed, respectively. Within 10 days of dosing, approximately 80% of the total loratadine administered were found in equal proportions between the urine and feces in the form of metabolic products. Finally, loratadine is 97% plasma-protein bound.

The most common adverse side effects of loratadine therapy include headache, somnolence, fatigue, and dry mouth. Less common or rare side effects may include altered lacrimination, altered salivation, flushing, hypoesthesia, impotence, increased sweating, thirst, angioneurotic edema, asthenia, back pain, blurred vision, chest pain, earache, eye pain, fever, leg cramps, malaise, rigors, tinnitus, viral infection, weight gain, hypertension, hypotension, palpitations, superventricular tachyarrhythmias, syncope, tachycardia, blepharospasm, dizziness, dysphonia, hypertonia, migraine, paresthesia, tremor, vertigo, altered taste, anorexia, constipation, diarrhea, dyspepsia, flatulence, gastritis, hiccup, increased appetite, nausea, stomatitis, toothache, vomiting, arthraglia, myalgia, agitation, amnesia, anxiety, confusion, decreased libido, depression, impaired concentration, insomnia, irritability, paroniria, breast pain, dysmenorrhea, menorrhagia, vaginitis, bronchitis, bronchospasm, coughing, dyspnea, epistaxis, hemoptysis, laryngitis, nasal dryness, pharyngitis, sinusitis, sneezing, dermatitis, dry hair, dry skin, photosensitivity reaction, pruritis, purpura, rash, urticaria, altered micturition, urinary discoloration, urinary incontinence, urinary retention. Further, the following spontaneous adverse effects were rarely reported for loratadine: abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis, alopecia, anaphylaxis, breast enlargement, erythema multiforme, peripheral edema, and seizures. (Physicians' Desk Reference, 53rd Edition, 1999, hereby incorporated by reference).

Despite advances in the art, there remains a need for methods of treating patients with seasonal allergic rhinitis and chronic idiopathic urticaria with an agent that provides effective

levels of loratadine for prolonged periods of time, preferably while eliminating or minimizing the symptoms of seasonal allergic rhinitis or chronic idiopathic urticaria, and/or any of the other above mentioned side effects, thus providing a safe and effective method of management of such allergic reactions and skin disorders.

Objects and Summary of the Invention

It is an object of the present invention to provide a continuous plasma loratadine concentration in mammals, preferably humans patients suffering from seasonal allergic rhinitis and/or chronic idiopathic urticaria.

It is an object of certain embodiments of the present invention to provide a method for treating patients suffering from seasonal allergic rhinitis and chronic idiopathic urticaria which achieves prolonged and effective management of these conditions, while at the same time provides the opportunity to reduce possible side effects, e.g., which patients may experience when subjected to prolonged oral therapy.

It is an object of certain embodiments of the present invention to provide a method for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria disorders in patients by utilizing a transdermal delivery system which contains loratadine.

It is an object of certain embodiments of the present invention to provide a method for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria disorders in patients which maximizes the dosage interval, i.e., the interval during which the transdermal delivery system is maintained in contact with the skin, and minimizes the plasma concentrations and or fluctuations in plasma concentrations in the patients during the dosage interval, while surprisingly maintaining effective management of seasonal allergic rhinitis and chronic idiopathic urticaria.

It is an object of certain embodiments of the present invention to provide a method for lessening the dry mouth associated with the oral administration of loratadine.

In certain embodiments, the present invention is directed to a method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient, comprising

administering loratadine transdermally to the human patient by applying a transdermal delivery system containing loratadine to the skin of a patient, and maintaining the transdermal delivery system in contact with the skin of the patient for at least 3 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the loratadine within 36 hours from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the three-day dosing interval.

In certain embodiments, the present invention is directed to a method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient, comprising

administering loratadine transdermally to the human patient by applying a transdermal delivery system containing loratadine to the skin of a patient, and maintaining the transdermal delivery system in contact with the skin of the patient for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

In certain embodiments, the present invention is directed to a method for lessening the incidence of side-effects in a patient associated with the oral administration of loratadine, wherein the method comprises administering the loratadine in a transdermal delivery system over at least twenty-four hours and thereby lessening the incidence of side effects.

In certain embodiments, the above methods can further comprise providing a mean relative release rate of loratadine from a transdermal delivery system to provide a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours, 3 hours, 2 hours, 1 hour or 0.5 hours after after application of the transdermal delivery system onto the skin of the patient.

In certain embodiments, the above methods can further comprise providing a loratadine transdermal delivery system which maintains a plasma level of loratadine at steady-state from about 1 to about 3 ng/ml.

In certain embodiments, the above methods can further comprise maintaining a therapeutic plasma level from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for the transdermal delivery system.

In certain embodiments, the above methods can further comprise having the transdermal delivery system having a mean relative release rate from 1.0 μm/hour/cm^2 to about 30.0 μm/hour/cm^2 or about 1.8 μm/hour/cm^2 to about 17 μm/hour/cm^2.

In certain other embodiments, the above methods can further comprise having the transdermal delivery system having a mean relative release rate from 2.0 μm/hour/cm^2 to about 10.0 μm/hour/cm^2.

In certain other embodiments, the above methods can further comprise having the transdermal delivery system having a mean relative release rate from 2.0 μm/hour/cm^2 to about 5.0 μm/hour/cm^2.

In certain embodiments, the above methods can further comprise having the transdermal delivery system having a mean relative release rate from about 2.8 μg/cm^2/hr to about 16.2 μg/cm^2/hr at 24 hours;
from about 2.3 μg/cm^2/hr to about 13.7 μg/cm^2/hr at 48 hours; and
from about 2.0 μg/cm^2/hr to about 11.9 μg/cm^2/hr at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In certain embodiments, the above methods can further comprise having the transdermal delivery system to provide an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg//cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is

a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In certain embodiments, the above methods can further comprise having the plasma level of loratadine at 48 hours not decrease by more than 30% over the next 72 hours.

In certain embodiments, the above methods can further comprise maintaining an effective mean relative release rate of the transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval.

In certain embodiments, the above methods can further comprise administering the loratadine in a transdermal delivery system applied to the skin of a human patient for about 3 to about 5 days.

In certain embodiments, the invention is directed to a transdermal device containing loratadine which provides effective blood plasma levels of loratadine when the device is applied to the skin of a mammal, preferably a human.

In certain embodiments, the invention is directed to a transdermal device containing loratadine which provides effective treatment of seasonal allergic rhinitis and chronic idiopathic urticaria disorders in patients.

In certain embodiments, the invention is directed to a transdermal delivery device comprising loratadine or a pharmaceutically acceptable salt thereof which maintains an effective mean relative release rate to provide a therapeutic blood level of the loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

In certain embodiments, the invention is directed to a transdermal device containing loratadine for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria disorders in patients which maximizes the dosage interval, i.e., the interval during which the

transdermal delivery system is maintained in contact with the skin, and minimizes the plasma concentrations and or fluctuations in plasma concentrations in the patients during the dosage interval, while surprisingly maintaining effective management of seasonal allergic rhinitis and chronic idiopathic urticaria.

In certain embodiments, the invention is directed to a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof which provides a mean relative release rate from about 1.0 μm/hour/cm^2 to about 30.0 μm/hour/cm^2 or about 1.8 μm/hour/cm^2 to about 17 μm/hour/cm^2 of the transdermal delivery system; a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours, 3 hours, 2 hours, 1 hour or 0.5 hours after application of the transdermal delivery system onto the skin of the patient; and a plasma level of loratadine at steady-state from about 0.1 to about 3.3 ng/ml.

In certain embodiments, the transdermal delivery system provides a mean relative release rate from about 2.8 μg/cm^2/hr to about 16.2 μg/cm^2/hr at 24 hours; from about 2.3 μg/cm^2/hr to about 13.7 μg/cm^2/hr at 48 hours; and from about 2.0 μg/cm^2/hr to about 11.9 μg/cm^2/hr at 72 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In certain embodiments, the transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg/cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In certain embodiments, the transdermal delivery system maintains a plasma level of loratadine at steady-state from about 1 to about 3 ng/ml.

In certain embodiments, the transdermal delivery system maintains an effective mean relative release rate to provide a therapeutic blood level of the loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

In certain embodiments, the transdermal delivery system provides a mean relative release rate of loratadine effective to provide a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours, 3 hours, 2 hours, 1 hour or 0.5 hours after application of the transdermal delivery system onto the skin of the patient.

In certain embodiments, the transdermal delivery system maintains a plasma level of loratadine at steady-state from about 1 to about 3 ng/ml.

In certain embodiments, the transdermal delivery system maintains a therapeutic plasma level from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for the transdermal delivery system.

In certain embodiments, the transdermal delivery system provides a mean relative release rate from about 1.0 μm/hour/cm^2 to about 30.0 μm/hour/cm^2 or about 1.8 μg/hour/cm^2 to about 17 μg/hour/cm^2 of the transdermal delivery system.

In certain embodiments, the transdermal delivery system provides a mean relative release rate from about 2.8 μg/cm^2/hr to about 16.2 μg/cm^2/hr at 24 hours; from about 2.3 μg/cm^2/hr to about 13.7 μg/cm^2/hr at 48 hours; and from about 2.0 μg/cm^2/hr to about 11.9 μg/cm^2/hr at 72 hours; and from about 1.8 μg/cm^2/hr to about 9.9 μg/cm^2/hr at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In certain embodiments, the transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63 μg/cm^2 to about 388 μg/cm^2 at 24 hours; from about 105 μg/cm^2 to about 660 μg/cm^2 at 48 hours; and from about 139 μg/cm^2 to about 854 μg/cm^2 at 72 hours; and from about 162 μg/cm^2 to about 955 μg/cm^2 at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and the cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

In further embodiments, the invention is directed to a transdermal device and method which, when applied to the skin of a mammal such as a human patient, provides

therapeutically effective blood plasma levels of loratadine to effectively treat seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, wherein the transdermal device is maintained in contact with the patient's skin for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of the loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval.

The invention is further directed to a transdermal loratadine device for the effective treatment of seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, which device, when applied to the skin of a patient maintained in contact with the patient's skin for at least 3 days, has an effective mean relative release rate to provide a therapeutic blood level of the loratadine within 36 hours from the initiation of the dosing interval, and thereafter maintains a therapeutic blood level until the end of at least the three-day dosing interval.

The invention is further directed in part to a transdermal loratadine device for the treatment of chronic allergic rhinitis and chronic idiopathic urticaria which provides substantially zero order pharmacokinetics over a significant portion of the dosage interval.

The invention is further directed to a transdermal device and a method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, comprising applying the transdermal loratadine device to the skin of the patient and maintaining the transdermal delivery system in contact with the skin of a patient for at least 5 days, the transdermal delivery system maintaining an effective mean relative release rate to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval.

The invention is further directed to a transdermal loratadine device which when applied to the skin of a patient and maintained in contact with the patient's skin for at least 3 days, has an effective mean relative release rate to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 24 hours after

the initiation of the dosing interval; and thereafter provides an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the three-day dosing interval.

The invention is further directed to a transdermal loratadine device and a method for lessening the incidence of side-effects in a patient associated with the oral administration of loratadine, wherein the method comprises administering the loratadine in a transdermal dosage form over at least twenty-four hours and thereby lessening the incidence of side effects.

The invention is further directed to a transdermal loratadine device and method which provides for reduced side-effects and for avoids peak plasma concentrations of loratadine in a patient associated with the oral administration of loratadine (i.e., reduces the peak plasma level relative to immediate release orally delivered loratadine), via the administration of loratadine in a transdermal dosage form over at least twenty-four hours, thereby lessening the incidence of side effects and avoiding the peak plasma concentrations of loratadine.

In certain embodiments, the invention is directed to transdermal delivery devices which are suitable for attaining any of the above methods.

For example, the above methods can be achieved utilizing a transdermal therapeutic system for the administration of loratadine to the skin comprising a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer by weight comprising 20 to 90% of a polymeric matrix, 0.1 to 30% of a softening agent, 0.1 to 20% of loratadine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% of a solvent for the loratadine or salt thereof.

Another alternative is to utilize a laminated composite for administering loratadine or a pharmaceutically acceptable salt thereof to an individual transdermally comprising
(a) a polymer backing layer that is substantially impermeable to loratadine or the pharmaceutically acceptable salt thereof; and
(b) a reservoir layer comprising an acrylate or silicone pressure-sensitive adhesive, 0.1 to 20% of loratadine base or of a pharmaceutically acceptable salt thereof, 0.1 to 30% of an

ester of a carboxylic acid acting as a softening agent and 0.1 to 30% of a solvent for loratadine having at least one acidic group.

The methods of the present invention are described in further detail in the following sections. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention pertains. However, it should be understood that for purposes of the present invention, the following terms have the following meanings:

The term "effective treatment of seasonal allergic rhinitis or chronic idiopathic urticaria" is defined for purposes of the present invention as a satisfactory reduction in or elimination of the symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria, along with the process of a tolerable level of side effects, as determined by the human patient.

Drug release from membrane-controlled systems may be defined as follows:

*Amount released per area unit Q = const (*zero order kinetics)

The term "mean relative release rate" is determined from the amount of drug released per unit time from the transdermal delivery system through the skin and into the bloodstream of a human patient. Mean relative release rate may be expressed, e.g., as $\mu g/cm^2/hr$. For example, a transdermal delivery system that releases 10 mg of loratadine over a time period of 24 hours is considered to have a relative release rate of 420 $\mu g/hr$. For purposes of the invention, it is understood that relative release rates may change between any particular time points within a particular dosing interval, and the term therefore only reflects the overall release rate during the particular dosing interval. For purposes of the present invention, relative release rate should be considered synonymous with the term "flux rate".

The term "sustained release" is defined for purposes of the present invention as the release of the drug (loratadine) from the transdermal formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective concentration) but below the upper limit of the therapeutic window over a period of time of about 3 days or longer.

The term "steady state" means that the blood plasma concentration curve for a given drug has been substantially repeated from dose to dose.

The term "minimum effective concentration" is defined for purposes of this invention as the minimum effective therapeutic blood plasma level of the drug at which at least some therapeutic effect in treating seasonal allergic rhinitis or chronic idiopathic urticaria is achieved in a given patient.

The term "overage" means for the purposes of the present invention the amount of loratadine contained in a transdermal delivery system which is not delivered to the patient. The overage is necessary for creating a concentration gradient by means of which the active agent (e.g., loratadine) migrates through the layers of the transdermal dosage form to the desired site on a patient's skin.

The term "first order" pharmacokinetics is defined as plasma concentrations which increase over a specified time period.

The term "zero order" pharmacokinetics contemplates an amount of drug released from a loratadine formulation which substantially maintains plasma concentrations at a relatively constant level. For purposes of the present invention, a relatively constant plasma concentration is defined as a concentration which does not decrease more than about 30% over a 48 hour time period.

Drug release from membrane-controlled systems may be defined as follows:

*Amount released per area unit Q = const (*zero order kinetics)

The term "mean relative release rate" is determined from the amount of drug released per unit time from the transdermal delivery system through the skin and into the bloodstream of a human patient. Mean relative release rate may be expressed, e.g, as $\mu g/cm^2/hr$. For example, a transdermal delivery system that releases 10 mg of loratadine over a time period of 24 hours is considered to have a relative release rate of $4.1 \times 10^{-4} \mu g/hr$. For purposes of the invention, it is understood that relative release rates may change between any particular time points within a particular dosing interval, and the term therefore only reflects the overall release rate during the particular dosing interval. For purposes of the present invention, relative release rate should be considered synonymous with the term "flux rate".

The term "sustained release" is defined for purposes of the present invention as the release of the drug from the transdermal formulation at such a rate that blood (e.g., plasma) concentrations (levels) are maintained within the therapeutic range (above the minimum effective drug concentration or "MEDC") but below toxic levels over a period of time of about 3 days or longer.

The term "steady state" means that the blood plasma concentration curve for a given drug has been substantially repeated from dose to dose.

The term "minimum effective concentration" is defined for purposes of this invention as the minimum effective therapeutic blood plasma level of the drug at which at least some relief of the seasonal allergic rhinitis or chronic idiopathic urticaria symptoms is achieved in a given patient.

For purposes of the present invention, the term "loratadine" shall include loratadine base, pharmaceutically acceptable salts thereof, stereoisomers thereof, enantiomers thereof, ethers thereof, and mixtures thereof.

For purposes of the present invention, the terms "transdermal delivery device" and "transdermal delivery system" are interchangeable.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIG. 1 is a graphical representation of the cumulative amounts of loratadine resulting from 3 permeation tests of Example 1 through human cadaver skin.

FIG. 2 is a graphical representation of the average loratadine permeation rate (flux rate) of Example 2 through human cadaver skin.

FIG. 3 is a graphical representation of the average cumulative amount of loratadine resulting from 4 permeation tests of Example 2 through human cadaver skin.

FIG. 4 is a graphical representation of the cumulative amounts of loratadine resulting from 3 permeation tests of Example 3 through human cadaver skin.

FIG. 5 is a graphical representation of the cumulative amounts of loratadine resulting from 3 permeation tests of Example 4 through human cadaver skin.

FIG. 6 is graphical representation of the average loratadine permeation rates (flux rates) of Examples 5, 6, and 7 through human cadaver skin.

FIG. 7 is a graphical representation of the average cumulative amounts of loratadine resulting from permeation tests of Examples 5, 6, and 7 through human cadaver skin.

FIG. 8 is a graphical representation of the average cumulative amounts of loratadine resulting from permeation tests of Examples 8, 9, and 10 through human cadaver skin.

FIG. 9 is a graphical representation of the average loratadine permeation rates (flux rates) of Examples 8, 9, and 10 through human cadaver skin.

FIG. 10 is a graphical representation of the average cumulative amounts of loratadine resulting from permeation tests of Examples 11, 12, and 9 through human cadaver skin.

FIG. 11 is a graphical representation of the average cumulative amounts of loratadine resulting from permeation tests of Examples 13 and 14 through human cadaver skin.

FIG. 12 is a graphical representation of the average loratadine permeation rates (flux rates) of Examples 13 and 14 through human cadaver skin.

FIG. 13 is a graphical representation of the average cumulative amounts of loratadine resulting from permeation tests of Examples 15 and 16 through human cadaver skin.

FIG. 14 is a graphical representation of the average loratadine permeation rates (flux rates) of Examples 15 and 16 through human cadaver skin.

Detailed Description

Transdermal delivery of active agents is measured in terms of "relative release rate" or "flux", i.e., the rate of penetration of the active agent through the skin of an individual. Skin flux may be generally determined from the following equation:

$$dm/dT=J=P * C$$

where J is the skin flux, P is the permeability coefficient and C is the concentration gradient across the membrane, assumed to be the same as the donor concentration. M represents the amount of drug entering the blood stream. The variable dm/dT represents the change in the amount of drug entering the blood stream over time.

It is well understood in the art of transdermal delivery systems that in order to maintain a desired flux rate for a desired dosing period, it is necessary to include an overage of active agent in the transdermal delivery system in an amount that is substantially greater than the amount to be delivered to the patient over the desired time period. For example, to maintain the desired flux rate for a three day time period, it is considered necessary to include much greater than 100% of a three-day dose of an active agent in a transdermal delivery system. This overage is necessary for creating a concentration gradient by means of which the active agent migrates through the layers of the transdermal delivery system to the desired site on a patient's skin. The remainder of the active agent remains in the transdermal delivery system. It is only the portion of active agent that exits the transdermal delivery system that becomes available for absorption into the skin. The total amount of active agent absorbed into the patient's blood stream is less than the total amount available. The amount of overage to be included in a transdermal delivery system is dependent on these and other factors known to the skilled artisan.

It has been found that it is possible to treat seasonal allergic rhinitis and chronic idiopathic urticaria according to the present invention by providing a transdermal delivery system containing a sufficient amount of loratadine to provide a desired relative release rate for at least about 3 days, and after single administration (application) of the transdermal dosage form, leaving the dosage form on the skin for approximately a 3 to 8 day time period, thereby resulting in the flux being maintained over the prolonged period and effective blood plasma levels and management of seasonal allergic rhinitis or chronic idiopathic urticaria being maintained over the prolonged period. Preferably, the desired flux is maintained at least about 5, preferably at least about 7 days after application of the transdermal delivery system.

Transdermal dosage forms used in accordance with the invention preferably include a backing layer made of pharmaceutically acceptable material which is impermeable to loratadine. The backing layer preferably serves as a protective cover for the active agent, e.g. loratadine and may also provide a support function. Examples of materials suitable for making the backing layer are films of high and low density polyethylene, polypropylene, polyvinylchloride, polyurethane, polyesters such as poly(ethylene terephthalate), metal foils, metal foil laminates of such suitable polymer films, textile fabrics, if the components of the reservoir cannot penetrate the fabric due to their physical properties and the like. Preferably, the materials used for the backing layer are laminates of such polymer films with a metal foil such as aluminum foil. The backing layer can be any appropriate thickness which will provide the desired protective and support functions. A suitable thickness will be from about 10 to about 200 microns. Desirable materials and thickness will be apparent to the skilled artisan.

Matrix Systems

In certain preferred embodiments, the transdermal dosage forms used in accordance with the invention contain a polymer matrix layer. Generally, the polymers used to form the biologically acceptable polymer matrix are those capable of forming thin walls or coatings through which pharmaceuticals can pass at a controlled rate. A non-limiting list of exemplary materials for inclusion in the polymer matrix includes polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethylacrylate copolymers, ethylene vinyl acetate copolymers, silicones, rubber, rubber-like synthetic homo-, co- or block polymers, polyacrylic esters and the copolymers thereof, polyurethanes, polyisobutylene, chlorinated polyethylene, polyvinylchloride, vinyl chloride-vinyl acetate copolymer, polymethacrylate polymer (hydrogel), polyvinylidene chloride, poly(ethylene terephthalate), ethylene-vinyl alcohol copolymer, ethylene-vinyloxyethanol copolymer, silicones including silicone copolymers such as polysiloxane-polymethacrylate copolymers, cellulose polymers (e.g., ethyl cellulose, and cellulose esters), polycarbonates, polytetrafluoroethylene and mixtures thereof.

Preferred materials for inclusion in the polymer matrix layer are silicone elastomers of the general polydimethylsiloxane structures, (e.g., silicone polymers). Preferred silicone polymers cross-link and are pharmaceutically acceptable. Other preferred materials for inclusion in the polymer matrix layer include: silicone polymers that are cross-linkable

copolymers having dimethyl and/or dimethylvinyl siloxane units which can be crosslinked using a suitable peroxide catalyst. Also preferred are those polymers consisting of block copolymers based on styrene and 1,3-dienes (particularly linear styrene-isoprene-block copolymers of styrene-butadiene-block copolymers), polyisobutylenes, polymers based on acrylate and/or methacrylate.

The polymer matrix layer may optionally include a pharmaceutically acceptable cross-linking agent. Suitable crosslinking agents include, e.g., tetrapropoxy silane.

Preferred transdermal delivery systems used in accordance with the methods of the present invention include an adhesive layer to affix the dosage form to the skin of the patient for a desired period of administration, e.g., about 3 to about 8 days. If the adhesive layer of the dosage form fails to provide adhesion for the desired period of time, it is possible to maintain contact between the dosage form with the skin by, for instance, affixing the dosage form to the skin of the patient with an adhesive tape, e.g, surgical tape. It is not critical for purposes of the present invention whether adhesion of the dosage form to the skin of the patient is achieved solely by the adhesive layer of the dosage form or in connection with a peripheral adhesive source, such as surgical tape, provided that the dosage form is adhered to the patient's skin for the requisite administration period.

The adhesive layer preferably includes using any adhesive known in the art that is pharmaceutically compatible with the dosage form and preferably hypoallergenic, such as polyacrylic adhesive polymers, acrylate copolymers (e.g., polyacrylate) and polyisobutylene adhesive polymers. In other preferred embodiments of the invention, the adhesive is a pressure-sensitive contact adhesive, which is preferably hypoallergenic.

The transdermal dosage forms which can be used in accordance with the present invention may optionally include a permeation enhancing agent. Permeation enhancing agents are compounds which promote penetration and/or absorption of the loratadine into the blood stream of the patient. A non-limiting list of permeation enhancing agents includes polyethylene glycols, surfactants, and the like.

Alternatively, permeation of loratadine may be enhanced by occlusion of the dosage form after application to the desired site on the patient with, e.g. an occlusive bandage. Permeation may also be enhanced by removing hair from the application site by, e.g. clipping, shaving or use of a depilatory agent. Another permeation enhancer is heat. It is

thought that heat enhancement can be induced by, among other things, using a radiating heat form, such as an infrared lamp, onto the application site after application of the transdermal dosage form. Other means of enhancing permeation of loratadine such as the use of iontophoretic means are also contemplated to be within the scope of the present invention.

A preferred transdermal dosage form which may be used in accordance with the present invention includes a non-permeable backing layer made, for example, of polyester; an adhesive layer made, for example of a polyacrylate; and a matrix containing the loratadine and other desirable pharmaceutical aids such as softeners, permeability enhancers, viscosity agents and the like.

The active agent may be included in the device in a drug reservoir, drug matrix or drug/adhesive layer. Preferably, the active agent is loratadine or a pharmaceutically acceptable salt thereof.

Certain preferred transdermal delivery systems also include a softening agent. Suitable softening agents include higher alcohols such as dodecanol, undecanol, octanol, esters of carboxylic acids, wherein the alcohol component may also be a polyethoxylated alcohol, diesters of dicarboxylic acids, such as di-n-butyladiapate, and triglycerides particularly medium-chain triglycerides of the caprylic/capric acids or coconut oil, have proved to be particularly suitable. Further examples of suitable softeners are multivalent alcohols, for example, levulinic acid, cocprylic acids glycerol and 1,2-propanediol which can also be etherified by polyethylene glycols.

A loratadine solvent may also be included in the transdermal delivery systems of the present invention. Preferably, the solvents dissolve the loratadine to a sufficient extent thereby avoiding complete salt formation. A non-limiting list of suitable solvents include those with at least one acidic group. Particularly suitable are monoesters of dicarboxylic acids such as monomethylglutarate and monomethyladipate.

Other pharmaceutically acceptable compounds which may be included in the reservoir or matrix include: solvents, for example alcohols such as isopropanol; permeation enhancing agents such as those described above; and viscosity agents, such as cellulose derivatives, natural or synthetic gums, such as guar gum, and the like.

In preferred embodiments, the transdermal dosage form includes a removable protective layer. The removable protective layer is removed prior to application, and consists of the materials used for the production of the backing layer described above provided that they are rendered removable, for example, by a silicone treatment. Other removable protective layers, for example, are polyltetra-fluoroethylene, treated paper, allophane, polyvinyl chloride, and the like. Generally, the removable protective layer is in contact with the adhesive layer and provides a convenient means of maintaining the integrity of the adhesive layer until the desired time of application.

The composition of the transdermal dosage forms used in accordance with the invention and the type of device used are not considered critical to the method of the invention, provided that the device delivers the active agent, e.g. loratadine, for the desired time period and at the desired flux rate and/or the desired delivery rate of the transdermal dosage form.

Certain transdermal dosage forms for use in accordance with the present invention are described in U.S. Patent No. 5,240,711 (Hille, *et. al.;* assigned to LTS Lohmann Therapie-Systeme GmbH & Co.), hereby incorporated by reference. Such transdermal delivery systems may be a laminated composite having an impermeable backing layer containing loratadine, e.g., instead of buprenorphine, and optionally a permeation enhancer combined with a pressure-sensitive adhesive. A preferred transdermal dosage form in accordance with the '711 patent includes: (i) a polyester backing layer which is impermeable to the drug; (ii) a polyacrylate adhesive layer; (iii) a separating polyester layer; and (iv) a matrix containing loratadine, a solvent for the loratadine, a softener and a polyacrylate adhesive. The loratadine solvent may or may not be present in the final formulation. The transdermal delivery device described therein includes a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer and optionally, a removable protective layer. Preferably, the reservoir layer includes about 10 to about 95%-wt polymeric material, about 0.1 to about 40%-wt softener, about 0.1 to about 30%-wt loratadine. A solvent for the loratadine base or pharmaceutically acceptable salt thereof may be included as about 0.1 to about 30%-wt.

The transdermal delivery system may also be prepared in accordance with the disclosure of International Patent Application No. WO 96/19975 (Hille, *et. al.;* assigned to LTS Lohmann Therapie-Systeme GMBH), hereby incorporated by reference, where

loratadine is substituted for buprenorphine as an active agent. In this device, the loratadine transdermal delivery device contains resorption-promoting auxiliary substances. The resorption-promoting auxiliary substance forms an undercooled mass. The delivery system contains 10% loratadine base, 10-15% acid (such as levulinic acid), about 10% softener (such as oleyoleate); 55-70% polyacrylate; and 0-10% polyvinylpyrollidone (PVP).

Reservoir Devices

Alternatively, the transdermal device may be a reservoir system. A reservoir system transdermal drug delivery patch comprises several different components. An exemplary construction includes a backing layer, an active drug and optional permeation enhancing solvent gel, a membrane, a skin contact adhesive layer, and a protective release coated liner film. Characteristics of each component are set forth below:

Backing Film: This layer is exposed to the external environment when the system is worn on the skin surface. It is impervious to penetration of the active drug contained within the system preventing the escape of the active drug through the backing film. The backing film serves as barrier layer. Moisture, soaps, lotions and other elements are prevented from entering the system and diluting the active ingredients or altering the release characteristics of the system. The active drug and solvent are contained within the system to perform its designated function. The backing film also forms one half of the chamber which contains the active drug reservoir. The backing film must be capable of being suitably attached to the membrane in order to form the reservoir chamber. Typical attachment methods include thermal, ultrasonic polymer heat seal or welding, and adhesive bonding. Necessary mechanical properties include a low compliance for conformability to the skin surface and elasticity to allow for movement with the skin surface. Typical thickness is in the range of 0.5 – 25.0 mil. A wide range of homogenous, woven, and non-woven polymer or composite materials are suitable as backing films.

Membrane: The membrane in combination with the backing film forms the chamber which contains the active drug reservoir. The membrane is attached to the backing film, and provides a support surface for the skin contact adhesive. The membrane can be a homogenous polymer film, or a material with a porous structure. The membrane may also be designed to control the transport rate of the active drug and/or the permeation enhancing solvent. Necessary mechanical properties include a low compliance for conformability to the skin surface and elasticity to allow for movement with the skin surface. Typical thickness is

in the range of 0.25 – 30.0 mil and more preferably in the range of 0.5 to 25.0 mils. A wide range of homogenous, porous, woven, and non-woven polymer or composite materials are suitable as membranes and known in the art.

Active Drug Reservoir: The active drug is combined with a liquid vehicle to fill the reservoir chamber. A range of solvents can be used for the liquid vehicle. The solvents can be chosen to optimize skin permeation of the active (enhancers) or to optimize the permeation characteristics of the membrane or the adhesion of the skin contact adhesive. A viscosity increasing agent is often included in the vehicle to aid in the handling and system manufacturing process. The composition of the vehicle must be compatible with the other components of the system. The vehicle may be in the form of a solution, suspension, cream, lotion, gel, physical mixture or emulsion. This list is not meant to be exhaustive.

Skin Contact Adhesive: The system is affixed to the skin with a skin contact adhesive. The adhesive may cover the entire surface of the system membrane, be applied in an intermittent pattern, or only to the perimeter of the system. The adhesive composition must be of materials suitable for skin contact without creating intolerable adverse effects such as excessive skin irritation or sensitization. Adequate adhesion to the membrane and skin are also necessary. The adhesive must also possess enough cohesive integrity to remain completely on the membrane upon removal of the system. The adhesive is applied in a thickness to provide a weight of 0.025 to 50.0 mg/cm^2, more preferably 0.25 to 1.0 mg/cm^2 and most preferably 0.3 to 0.6 mg/cm^2. Typical materials include silicone, polyisobutylene (PIB), and acrylates dissolved in organic solvents, aqueous emulsions, or directly applied by hot melt processing.

Release Coated Liner Film: The liner film is removed from the system before application to the skin surface. The liner film serves the function as a protective barrier to the skin contact adhesive prior to use. The coating on the liner provides a release capability for the adhesive, allowing separation of the liner from the adhesive. A coating is not necessary if the liner material is readily removed from the adhesive without disrupting the reservoir system. Typical thickness is in the range of 0.5 – 25.0 mil. A wide range of homogenous, woven, and non-woven paper, polymer or composite materials are suitable as liner films. Release coatings are typically composed of paraffin, polyethylene, silicone or fluorocarbons.

In other embodiments, the transdermal delivery system may be a plaster such as that described in U.S. Patent No. 5,225,199 to Hidaka *et al.*, hereby incorporated by reference. Such plasters include a film layer including a polyester film of about 0.5 to about 4.9 μm thickness, about 8 to about 85 g/mm strength, respectively in the two directions intersecting substantially at right angles, about 30 to about 150% elongation, in the two directions intersecting substantially at right angles and an elongation ratio of A to B of about 1.0 to about 5.0, wherein A and B represent data in two directions intersecting at right angles, and A is greater than B and wherein the polyester film includes about 0.01 to about 1.0% by weight, based on the total weight of the polyester film, of solid fine particles in which the average particle size is about 0.001 to about 3.0 μm and an adhesive layer which is composed of an adhesive containing transdermally absorbable drugs; wherein the adhesive layer is laminated on the film layer over the surface in about 2 to about 60 μm thickness. The average particle size is substantially not more than 1.5 times the thickness of the polyester film.

The transdermal delivery system used in the present invention may also be prepared in accordance with U.S. Patent No. 5,879,701, issued March 9, 1999 to Audett, *et al.*, hereby incorporated by reference, wherein solubilization enhancer compositions are provided which facilitate transdermal administration of basic drugs from transdermal systems composed of nonpolar adhesive materials. The solubilization enhancing composition is particularly useful in facilitating the administration of basic drugs using transdermal systems worn for at least four days containing drug reservoirs comprised of nonpolar materials such as polyisobutylene adhesives or the like. The solubilizing enhancing composition itself is preferably a liquid which is an isomeric acid mixture. Examples of suitable solubilizers include, but are not limited to, oleic acid dimer and neodecanoic acid, with oleic acid dimer particularly preferred. The solubilizer constitutes at least about 0.10 wt.% of the reservoir, and preferably represents on the order of 0.25 wt.% to 1.0 wt.% of the reservoir. The amount of enhancer composition present in the drug formulation will depend on a number of factors, e.g., the strength of the particular enhancer composition, the desired increase in skin permeability, and the amount of drug which is necessary to deliver.

The pharmacokinetic information for loratadine is available in the literature. The adult oral dosage for loratadine is 10 mg/day. The bioavailability for the drug is 20%, expressed as fraction, 0.20 of the oral dose made available to the blood stream from gastrointestinal absorption. A release rate for a loratadine transdermal delivery system was calculated from this data. 0.20 of the oral 10 mg daily dose provides 2.0 mg of loratadine

available into the blood stream. Therefore, an equal dose is required to be delivered transdermally. 2.0 mg/day is converted to 2000 mcg/24 hours. This would require delivery of 83.3 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 83.3 mcg/hour/40 cm^2 by 40, yields a release rate of 2.1 mcg/hour/cm^2 of transdermal patch surface area. To account for drug elimination, further pharmacokinetic data and physiological data was required. The plasma concentration at steady state for loratadine is 0.002 mcg/ml. The physiological clearance rate is 196,000 ml/hour. The dosing rate is obtained from the product of the steady state concentration of loratadine and a representative clearance rate. This product is 392 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 392 mcg/hour/40 cm^2 by 40, yields a release rate of 9.8 mcg/hour/cm^2 of transdermal patch surface area. One of skill would expect a larger input rate or flux to maintain a steady state concentration in consideration of the loss of drug in the plasma due to elimination. A confirmatory calculation for flux requires further pharmacokinetic parameters. The volume of distribution for loratadine is 1,660,000 ml and the half-life is 8.4 hours. The elimination rate constant is 0.693/half-life. The product of steady state concentration, volume of distribution and steady state concentration yields a rate of 274 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 274 mcg/hour/40 cm^2 by 40, yields a release rate of 9.8 mcg/hour/cm^2 of transdermal patch surface area.

Any type of transdermal delivery system may be used in accordance with the methods of the present invention so long as the desired pharmacokinetic and pharmacodynamic response(s) are attained over at least 3 days, e.g., from about 5 to about 8 days. Preferable transdermal delivery systems include e.g., transdermal patches, transdermal plasters, transdermal discs, iontophoretic transdermal devices and the like.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Overview of Method of Manufacture: Matrix System

The following general method is used in the following examples in which the transdermal device tested is a matrix system (device):

Step 1: Preparation of the active drug vehicle/solvent/adhesive matrix. Active drug is combined with the liquid vehicle components and the adhesive components using appropriate mixing techniques well known in the art. Simple mechanical mixers, motionless mixers, homogenizers, high shear mixers, and magnetic mixing devices can be employed.

Step 2: Preparation of the active drug/adhesive matrix coated liner. Active drug/adhesive matrix coating is done with continuous web based equipment on a commercial scale. Small sheet batches can be made readily in the lab manually. A mechanism for applying a controlled thickness coating of the active drug/adhesive matrix onto the liner is employed. If solvent-based adhesives are used, a procedure for driving off the solvent and drying the active drug/adhesive matrix is employed. The open surface of the active drug/adhesive matrix on the liner must be protected during processing. A second intermediate liner can be used to cover this active drug/adhesive matrix surface.

Step 3: Laminating of the membrane to active drug/adhesive and/or liner. The membrane is typically applied on line after solvent removal on a commercial scale. This avoids the need for a second liner. A separate web and a heat and/or pressure lamination station bonds the two layers. The membrane provides a non-stick surface to the open side of the adhesive and allows for further processing in a roll form.

Overview of the Manufacture of Reservoir Devices

The following general method is used in the following examples in which the transdermal device tested is a reservoir system (device):

Step 1: Preparation of the adhesive coated liner. Adhesive coating is done with continuous web based equipment on a commercial scale. Small sheet batches can be made readily in the lab manually. A mechanism for applying a controlled thickness coating of the adhesive onto the liner is employed. If solvent-based adhesives are used, a procedure for driving off the solvent and drying the adhesive is employed. The open surface of the adhesive on the liner must be protected during processing. A second intermediate liner can be used to cover this adhesive surface.

Step 2: Laminating of the membrane to adhesive and/or liner. The membrane is typically applied on line after solvent removal on a commercial scale. This avoids the need for a second liner. A separate web and a heat and/or pressure lamination station bonds the

two layers. The membrane provides a non-stick surface to the open side of the adhesive and allows for further processing in a roll form.

Step 3: Preparation of the active vehicle/solvent combination. Active drug is combined with the liquid vehicle components using appropriate mixing techniques well known in the art. Simple mechanical mixers, motionless mixers, homogenizers, high shear mixers, and magnetic mixing devices can be employed. Other ingredients are also incorporated at this time. These may include permeation enhancers and viscosity thickeners, for example.

Step 4: Finalizing the delivery system utilizing the form, fill and seal process incorporating the reservoir and backing film. This process can be carried out in either a horizontal or vertical plane. The horizontal mode requires a thickened viscosity of the reservoir vehicle, while the vertical mode can handle liquid vehicles of minimal viscosity. In the horizontal mode a dispensing head places a fixed volume drop of the drug vehicle onto the surface of the membrane. The backing film is then placed over the drop of vehicle, and then bound to the membrane to enclose the active/vehicle. A heated die is commonly used to form a heat seal welded bond. In web based systems a die cutting and packaging station often follows.

In-Vitro Skin Permeation Test Method

The test methods utilized in the following examples involves the use of a permeation cell. Several permeation cell designs are available for in-vitro permeation testing. These include "Franz cells", "Valia-Chien cells", and "Bronaugh cells". Each cell design shares several common characteristics. All cells are made with a definable surface area for permeation. All cells contain two chambers and a clamping mechanism to hold the test membrane positioned between the two cell chambers. Several exemplary test membranes include mouse skin and human cadaver skin. The membrane may be oriented in either the horizontal or vertical plane based on the cell special arrangement. One chamber serves as a reservoir (donor) for the drug to be tested, the second is a place where the permeated drug is accumulated (receptor). The receptor is often chosen to mimic the physiological conditions found beneath the membrane in-vivo. In the case where a complete transdermal system is the donor, it is clamped between the two chambers and only the receptor chamber is filled.

Calculation of the permeation rate (J) requires knowledge of the concentration (C) of the drug in the receptor chamber, the permeation area (A), sampling interval (t) and the receptor volume (V). The equation below is typical:

$J = CV / At$ where: J = micrograms/cm^2-hr
C = micrograms/ml
V = ml
A = cm^2
t = hr

Only the drug concentration and testing time vary in typical experiments. The drug concentration is determined by any appropriate analytical technique such as high performance liquid chromatograpy, gas chromatograpy, or ultraviolet spectrophotometry. Other considerations in the testing system may include temperature control systems, receptor stirring systems, flow through receptor chambers, and automated sampling equipment utilizing pumps and fraction collectors. Partial receptor sampling protocols have been used in situations where the sensitivity of the analytical method for determining the drug concentration was less than optimal.

Sample testing protocols for loratadine follow.

Cells	Valia Chien
Membrane	Human cadaver skin
A (cm2)	0.636
V (ml)	4.0
receptor	Ethanol/water 40/60
sampling points	6, 24, 48, 72, 120, 144, 168 hours
sampling mode:	partial, 0.6ml per point, replace with fresh receptor.

HPLC conditions for determination of drug concentration

Column	Altima C8, 5um, 4.6mm x 15cm
Mobile phase	Acetonitrile/Buffer 70/30
Buffer:	0.01M phosphate at pH 4.5
Flow rate	1 ml/min

UV detection	205 nm
Injection volume	20 microliters
Retention time	5.0 minutes

EXAMPLE 1

A Loratadine drug reservoir formulation was prepared having the formulation set forth in Table 1A below:

TABLE 1A

Ingredient	Amount (gm)
Loratadine	0.5
Ethanol	12.2
Water	15
Total	27.7
Ethylvinylacetate membrane	

The formulation of Table 1A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Loratadine is dissolved with ethanol and water and the solution is placed into the donor cell.
2. The ethylvinylacetate membrane is placed against the donor cell.
3. Thereafter, the human cadaver skin is placed between the membrane and the receptor cell and the apparatus is secured.

The formulation of Example 1 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (1-1, 1-2, 1-3) were conducted giving the results listed in Table 1B below:

TABLE 1B

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm^2 (μg/cm^2)
1-1	1	0.000	4	0.000	4	0.000	0.000	0.000	0.000
	2	0.177	4	0.708	4	0.708	0.000	0.708	1.113
	16	14.449	4	57.796	4	57.796	0.708	58.504	91.959
	17	0.914	4	3.656	4	3.656	58.504	62.160	97.705
	24	6.666	4	26.664	4	26.664	62.160	88.824	139.616
	42	18.644	4	74.576	4	74.576	88.824	163.400	256.837
	48	6.639	4	26.556	4	26.556	163.400	189.956	298.579
	168	120.233	4	480.932	4	480.932	189.956	670.888	1054.524
1-2	1	0.000	4	0.000	4	0.000	0.000	0.000	0.000
	2	0.154	4	0.616	4	0.616	0.000	0.616	0.968
	16	11.703	4	46.812	4	46.812	0.616	41.428	74.549
	17	0.433	4	1.732	4	1.732	47.428	49.160	77.271
	24	5.388	4	21.552	4	21.552	49.160	70.712	111.147
	42	15.636	4	62.544	4	62.544	70.712	133.256	209.456
	48	5.223	4	20.892	4	20.892	133.256	154.148	242.295
	168	113.298	4	453.192	4	453.192	154.148	607.340	945.637
1-3	1	0.000	4	0.000	4	0.000	0.000	0.000	0.000
	2	0.019	4	0.076	4	0.076	0.000	0.076	0.119
	16	10.734	4	42.936	4	42.936	0.076	43.012	67.608
	17	0.547	4	2.188	4	2.188	43.012	45.200	71.047
	24	4.741	4	18.964	4	18.964	45.200	64.064	100.855
	42	15.189	4	60.756	4	60.756	64.164	124.920	196.353
	48	4.950	4	19.800	4	19.800	124.920	144.720	227.476
	168	107.974	4	431.896	4	431.896	144.720	576.616	906.344

Based on the permeation results of Example 1, listed in Table 1B, the averages of the three tests were calculated and the flux results listed in Table 1C below were obtained:

TABLE 1C

Hours	Test 1-1	Test 1-2	Test 1-3	Avg. of all 3 tests	Std Dev	μg/cm²/hr
1	0.000	0.000	0.000	0.000	0.000	0.000
2	1.113	0.968	0.119	0.733	0.537	0.367
16	91.959	74.549	67.608	78.039	12.545	4.877
17	97.705	77.271	71.047	82.008	13.946	4.824
24	139.616	111.147	100.855	117.206	20.078	4.884
42	256.837	209.456	196.353	220.882	31.820	5.259
48	298.579	242.295	227.476	256.117	37.513	5.336
168	1054.524	954.637	906.344	971.835	75.572	5.785
F_{4-76}	**6.435**	**5.245**	**4.957**	**5.546**	**0.784**	
CORR	**1.000**	**1.000**	**0.999**	**1.000**		

EXAMPLE 2

A Loratadine reservoir and adhesive formulation was prepared having the formulation set forth in Table 2A below:

TABLE 2A

Ingredient	Amount (gm)
Loratadine	1.0
Ethanol	22.0
Water	27.0
Total	50.0
Polyethylene membrane	
Silicone adhesive	

The formulation of Table 2A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Loratadine is dissolved with ethanol and water and the solution is placed into the donor cell.
2. The polyethylene membrane is coated with a silicone adhesive and placed against the donor cell. The adhesive coated membrane is positioned opposite from the donor cell.
3. Thereafter, the human cadaver skin is placed between the adhesive coated polyethylene membrane and the receptor cell and the apparatus is secured.

The formulation of Example 2 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (2-1, 2-2, 2-3) were conducted giving the results listed in Table 2B below:

TABLE 2B

Hours	µg/cm²					
	Test 2-1	**Test 2-2**	**Test 2-3**	**Test 2-4**	**Avg. of all 4 tests**	**Std Dev**
6	5.608	7.362	6.344	4.231	5.886	1.317
24	87.325	83.930	66.665	66.771	76.173	11.005
30	125.489	120.132	91.229	92.763	107.406	17.936
48	228.840	220.207	158.202	165.954	193.307	36.363
54	271.600	262.829	183.313	193.688	227.858	45.783
72	381.257	368.375	249.607	269.632	317.218	67.215
78	425.099	409.871	273.618	297.447	351.509	77.053
96	544.508	521.226	343.427	375.668	446.207	101.375
102	592.644	565.193	368.375	404.470	482.671	112.669
120	715.385	675.064	436.674	483.691	577.704	138.037
144	892.983	836.158	536.473	598.510	716.031	174.924
168	1046.419	982.364	627.249	701.572	839.401	205.994

Based on the permeation results of Example 2, listed in Table 2B, the following flux results listed in Table 2C below were obtained:

TABLE 2C

Hours	µg/cm²/hr					
	Test 2-1	**Test 2-2**	**Test 2-3**	**Test 2-4**	**Avg. of all 4 tests**	**Std Dev**
6	0.935	1.224	1.057	0.705	0.981	0.220
24	3.639	3.497	2.778	2.782	3.174	0.459
30	4.183	4.004	3.041	3.092	3.580	0.598
48	4.768	4.588	3.296	3.457	4.027	0.758
54	5.030	4.867	3.395	3.587	4.220	0.848
72	5.295	5.116	3.467	3.745	4.406	0.934
78	5.450	5.255	3.508	3.813	4.507	0.988
96	5.672	5.429	3.577	3.913	4.648	1.056
102	5.810	5.541	3.612	3.965	4.732	1.105
120	5.962	5.626	3.639	4.031	4.814	1.150
144	6.201	5.807	3.726	4.156	4.972	1.215
168	6.229	5.847	3.734	4.176	4.996	1.226
F_{6-96}	**6.066**	**5.815**	**3.770**	**4.173**	**4.956**	**1.153**
CORR	**0.998**	**0.998**	**1.000**	**0.999**	**0.999**	

EXAMPLE 3

A Loratadine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 3A below:

TABLE 3A

Ingredient	Amount (gm)
Loratadine	0.23
Ethyl Acetate	1.77
BIO PSA 7-4302 (adhesive solution) containing 9.8 gm silicone adhesive (60% solids)	16.3
Total	18.3

The formulation of Table 3A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Loratadine is dispersed in the requisite amount of ethyl acetate and adhesive solution to form the active drug/adhesive matrix.
2. The active drug/adhesive matrix is applied to a backing layer and dried.
3. Thereafter, the patch is applied to the human cadaver skin affixed to the receptor cell.

The formulation of Example 3 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was ethanol:water (40:60) and the membrane was a human cadaver skin membrane. Three permeation tests (3-1, 3-2, 3-3) were conducted giving the results listed in Table 3B below:

TABLE 3B

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm^2 ($\mu g/cm^2$)
3-1	4	3.220	13	41.860	1	3.220	0.000	41.860	23.690
	24	34.978	13	454.714	1	34.978	3.220	457.934	259.159
	28	35.903	13	466.739	1	35.903	38.198	504.937	285.759
	48	55.584	13	722.592	1	55.584	74.101	796.693	450.873
	52	49.609	13	644.917	1	49.609	129.685	774.602	438.371
	72	60.990	13	792.870	1	60.990	179.294	972.164	550.178
	76	54.504	13	708.552	1	54.504	240.284	948.836	536.976
	96	61.080	13	794.040	1	61.080	294.788	1088.828	616.201
3-2	4	4.782	13	62.166	1	4.782	0.000	62.166	35.182
	24	37.018	13	481.234	1	37.018	4.782	486.016	275.051
	28	38.489	13	500.357	1	38.489	41.800	542.157	306.823
	48	54.826	13	712.738	1	54.826	80.289	793.027	448.799
	52	54.818	13	712.634	1	54.818	135.115	847.749	479.767
	72	61.280	13	796.640	1	61.280	189.933	986.573	558.332
	76	59.295	13	770.835	1	59.295	251.213	1022.048	578.409
	96	60.455	13	785.915	1	60.455	310.508	1096.423	620.500
3-3	4	2.418	13	31.434	1	2.418	0.000	31.434	17.789
	24	30.875	13	401.375	1	30.875	2.418	403.793	228.519
	28	33.696	13	438.048	1	33.696	33.293	471.341	266.746
	48	51.182	13	665.366	1	51.182	66.989	732.355	414.462
	52	50.819	13	660.647	1	50.819	118.171	778.818	440.757
	72	59.651	13	775.463	1	59.651	168.990	944.453	534.495
	76	55.812	13	725.556	1	55.812	228.641	954.197	540.010
	96	63.094	13	820.222	1	63.094	284.453	1104.675	625.170

Based on the permeation results of Example 3, listed in Table 3B, the averages of all three tests were calculated and the flux results listed in Table 3C below were obtained:

TABLE 3C

Hours	Test 3-1	Test 3-2	Test 3-3	Avg. of all 3 tests	Std Dev	µg/cm²/hr
4	23.690	35.182	17.789	25.554	8.845	6.388
24	259.159	275.051	228.519	254.243	23.652	10.593
28	285.759	306.823	266.746	286.443	20.047	10.230
48	450.873	448.799	414.462	438.045	20.449	9.123
52	438.371	479.767	440.757	452.965	23.242	8.711
72	550.178	558.332	534.495	547.668	12.115	7.607
76	536.946	578.409	540.010	551.798	23.095	7.261
96	616.201	620.500	625.170	620.624	4.486	6.465
F_{4-76}	**6.917**	**7.120**	**7.069**	**7.036**	**0.015**	
CORR	**0.970**	**0.975**	**0.982**	**0.976**		

EXAMPLE 4

A Loratadine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 4A below:

TABLE 4A

Ingredient	Amount (gm)
Loratadine	0.23
Ethyl Acetate	1.77
DURO-TAK 87-6430 (adhesive solution) containing 9.8 gm Polyisobutylene adhesive (30% solids)	32.6
Total	34.6

The formulation of Table 4A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3, using DURO-TAK 87-6430 as the adhesive solution.

The formulation of Example 4 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was ethanol:water (40:60). Three permeation tests (4-1, 4-2, 4-3) were conducted giving the results listed in Table 4B below:

TABLE 4B

Test #	Sampling Time (Hours)	Drug Conc. (µg/ml)	Receptor Volume (ml)	Drug Amount (µg)	Sampling Volume (ml)	Drug Loss due to Sampling (µg)	Cumulative Drug Loss (µg)	Cumulative Amount Permeated (µg)	Amount Permeated per cm^2 (µg /cm^2)
4-1	4	0.750	13	9.750	1	0.750	0.000	9.750	5.518
	24	8.590	13	111.670	1	8.590	0.750	112.420	63.622
	28	9.430	13	122.590	1	9.430	9.340	131.930	74.663
	48	13.706	13	178.178	1	13.706	18.770	196.945	111.459
	52	12.916	13	167.908	1	12.916	32.476	200.384	113.404
	72	15.903	13	206.739	1	15.903	45.392	252.131	142.689
	76	15.470	13	201.110	1	15.470	61.295	262.405	148.503
	96	16.762	13	217.906	1	16.762	76.765	294.671	166.763
4-2	4	0.468	13	6.084	1	0.468	0.000	6.084	3.443
	24	8.485	13	110.305	1	8.485	0.468	110.773	62.690
	28	8.718	13	113.334	1	8.718	8.953	122.287	69.206
	48	12.944	13	168.272	1	12.944	17.671	185.943	105.231
	52	11.946	13	155.298	1	11.946	30.615	185.913	105.214
	72	15.568	13	202.384	1	15.568	42.561	244.945	138.622
	76	14.784	13	192.192	1	14.784	58.129	250.321	141.664
	96	16.423	13	213.499	1	16.423	72.913	286.412	162.089
4-3	4	0.660	13	8.580	1	0.660	0.000	8.580	4.856
	24	9.734	13	126.542	1	9.734	0.660	127.202	71.988
	28	9.973	13	129.649	1	9.973	10.394	140.043	79.255
	48	14.864	13	193.232	1	14.864	20.367	213.599	120.882
	52	13.830	13	179.790	1	13.830	35.231	215.021	121.687
	72	17.243	13	224.159	1	17.243	49.061	273.220	154.624
	76	16.208	13	210.704	1	16.208	66.304	277.008	156.767
	96	18.495	13	240.435	1	18.495	82.512	322.947	182.766

Based on the permeation results of Example 4, listed in Table 4B, the averages of all three tests were calculated and the flux results listed in Table 4C below were obtained:

TABLE 4C

Hours	Test 4-1	Test 4-2	Test 4-3	Avg. of all 3 tests	Std Dev	μg/cm²/hr
4	5.518	3.443	4.856	4.606	1.060	1.151
24	63.622	62.690	71.988	66.100	5.120	2.754
28	74.663	69.206	79.255	74.375	5.031	2.656
48	111.459	105.231	120.882	112.524	7.880	2.344
52	113.404	105.214	121.687	113.435	8.237	2.181
72	142.689	138.622	154.624	145.312	8.317	2.018
76	148.503	141.664	156.767	148.978	7.563	1.960
96	166.763	162.089	182.766	170.539	10.843	1.776
F_{4-76}	**1.881**	**1.820**	**2.006**	**1.902**	**0.095**	
CORR	**0.983**	**0.984**	**0.979**	**0.982**		

EXAMPLE 5

A Loratadine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 5A below:

TABLE 5A

Ingredient	Amount (gm)
Loratadine	0.23
Ethyl Acetate	1.77
DURO-TAK 87-8298 (adhesive solution) containing 9.8 gm acrylate adhesive (38.5% solids)	28.8
Total	30.8

The formulation of Table 5A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3, using DURO-TAK 87-8298 as the adhesive solution.

The formulation of Example 5 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Two permeation tests (5-1, 5-2) were conducted giving the results listed in Table 5B below:

TABLE 5B

Test #	Sampling Time (Hours)	Drug Conc. (µg/ml)	Receptor Volume (ml)	Drug Amount (µg)	Sampling Volume (ml)	Drug Loss due to Sampling (µg)	Cumulative Drug Loss (µg)	Cumulative Amount Permeated (µg)	Amount Permeated per cm^2 (µg/cm^2)
5-1	6	1.828	12	21.936	1	1.828	0.000	21.936	12.414
	24	11.188	12	134.256	1	11.188	1.828	136.08	77.014
	48	22.197	12	266.364	1	22.197	13.016	279.38	157.110
	72	30.850	12	370.200	1	30.850	35.213	405.41	229.436
	96	36.048	12	432.576	1	36.048	66.063	498.64	282.195
	120	39.128	12	469.536	1	39.128	102.111	571.65	323.513
	148	39.190	12	470.280	1	39.190	141.239	611.52	346.078
	168	39.347	12	472.164	1	39.347	180.429	652.59	369.323
5-2	6	0.767	12	9.204	1	0.767	0.000	9.20	5.209
	24	6.015	12	72.180	1	6.015	0.767	72.95	41.283
	48	12.141	12	145.692	1	12.141	6.782	152.47	86.290
	72	17.910	12	214.920	1	17.910	18.923	233.84	132.339
	96	21.591	12	259.092	1	21.591	36.833	295.93	167.473
	120	24.647	12	295.764	1	24.647	58.424	354.19	200.446
	148	27.851	12	334.212	1	27.851	83.071	417.28	236.153
	168	29.933	12	359.196	1	29.933	110.922	470.12	266.054

The average of the two permeation tests of Example 5 was calculated and is listed in Table 5C below:

TABLE 5C

µg/cm^2				
Hours	Test 5-1	Test 5-2	Average of two tests	Std Dev
6	12.414	5.209	8.812	5.095
24	77.014	41.283	59.149	25.266
48	158.110	86.290	122.200	50.784
72	229.436	132.339	180.888	68.658
96	282.195	167.473	224.834	81.121
120	323.513	200.446	261.980	87.022
148	346.078	236.153	291.116	77.729
168	369.323	266.054	317.689	73.022

Based on the permeation results of Example 5, listed in Table 5B, the following flux results listed in Table 5D below were obtained:

TABLE 5D

μg/cm²/hr				
Hours	**Test 5-1**	**Test 5-2**	**Average of two tests**	**Std Dev**
6	2.069	0.868	1.469	0.846
24	3.209	1.720	2.465	1.053
48	3.294	1.798	2.546	1.058
72	3.187	1.838	2.512	0.954
96	2.940	1.745	2.342	0.845
120	2.696	1.670	2.183	0.725
148	2.338	1.596	1.967	0.525
168	2.198	1.584	1.891	0.435
F_{6-96}	**3.025**	**1.820**	**2.423**	**0.853**
CORR	**0.996**	**0.999**	**0.997**	**0.002**

EXAMPLE 6

A Loratadine active matrix/adhesive matrix formulation was prepared having the formulation set forth in Table 6A below:

TABLE 6A

Ingredient	Amount (gm)
Loratadine	0.36
Ethyl Acetate	2.67
BIO PSA 7-4302 (adhesive solution) containing 11.96 gm silicone adhesive (60 % solids)	19.93
Total	22.96

The formulation of Table 6A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3.

The formulation of Example 6 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (6-1, 6-2, and 6-3) were conducted giving the results listed in Table 6B below:

TABLE 6B

$\mu g/cm^2$					
Hours	**Test 6-1**	**Test 6-2**	**Test 6-3**	**Average of three tests**	**Std Dev**
6	103.382	105.542	89.338	99.421	8.798
24	385.736	387.593	348.952	374.094	21.793
48	637.848	659.757	591.666	629.757	34.759
72	832.501	854.233	769.620	818.785	43.942
96	897.573	954.671	857.260	903.168	48.946
124	972.628	1026.660	933.732	977.673	46.669
144	1041.228	1107.161	1003.008	1050.466	52.687
168	1051.728	1140.184	1036.631	1076.181	55.940

Based on the permeation results of Example 6, listed in Table 6B, the following flux results listed in Table 6C below were obtained:

TABLE 6C

$\mu g/cm^2/hr$					
Hours	**Test 6-1**	**Test 6-2**	**Test 6-3**	**Average of three tests**	**Std Dev**
6	17.230	17.590	14.890	16.570	1.466
24	16.072	16.150	14.540	15.587	0.908
48	13.289	13.745	12.326	13.120	0.724
72	11.563	11.864	10.689	11.372	0.610
96	9.350	9.944	8.930	9.408	0.510
124	7.844	8.280	7.530	7.884	0.376
144	7.231	7.689	6.965	7.295	0.366
168	6.260	6.787	6.170	6.406	0.333
F_{6-96}	**8.831**	**9.407**	**8.499**	**8.912**	**0.459**
CORR	**0.970**	**0.977**	**0.976**	**0.974**	**0.004**

EXAMPLE 7

A Loratadine active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 7A below:

TABLE 7A

Ingredient	Amount (gm)
Loratadine	0.24
Polyisobutylene (adhesive)	
MA-24 + mineral oil (adhesive solution) (25 % solids)	28.62
Total	28.86

The formulation of Table 7A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3, using MA-24 + mineral oil as the adhesive solution and without the use of ethyl acetate.

The formulation of Example 7 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (7-1, 7-2, and 7-3) were conducted giving the results listed in Table 7B below:

TABLE 7B

	$\mu g/cm^2$				
Hours	Test 7-1	Test 7-2	Test 7-3	Average of three tests	Std Dev
6	16.075	2.405	15.945	11.475	7.855
24	99.938	67.530	113.135	93.534	23.467
48	214.922	184.259	249.768	216.316	32.777
72	310.962	294.490	354.921	320.124	32.240
96	334.402	323.299	388.632	348.778	34.958
124	350.720	342.504	415.032	369.419	39.715
144	360.886	352.968	420.276	378.043	36.788
168	359.021	358.228	421.273	379.507	36.172

Based on the permeation results of Example 7, listed in Table 7B, the following flux results listed in Table 7C below were obtained:

TABLE 7C

μg/cm²/hr					
Hours	Test 7-1	Test 7-2	Test 7-3	Average of three tests	Std Dev
6	2.679	0.401	2.658	1.913	1.309
24	4.164	2.814	4.714	3.897	0.978
48	4.478	3.839	5.204	4.507	0.683
72	4.319	4.090	4.929	4.446	0.434
96	3.483	3.368	4.048	3.633	0.364
124	2.828	2.762	3.347	2.979	0.320
144	2.506	2.451	2.919	2.625	0.255
168	2.137	2.132	2.508	2.259	0.215
F_{6-96}	**3.697**	**3.802**	**4.305**	**3.934**	**0.325**
CORR	**0.979**	**0.985**	**0.981**	**0.981**	**0.003**

EXAMPLE 8

A active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 8A below:

TABLE 8A

Ingredient	Amount (gm)
Loratadine	0.12
Ethyl Acetate	0.89
Silicone (adhesive)	11.49 (60 % solids)
BIO PSA 7-4302 (adhesive solution)	19.14
Total	20.15

The formulation of Table 8A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3.

The formulation of Example 8A was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (8-1, 8-2, and 8-3) were conducted giving the results listed in Table 8B below:

TABLE 8B

μg/cm²					
Hours	**Test 8-1**	**Test 8-2**	**Test 8-3**	**Average of three tests**	**Std Dev**
6	49.508	21.195	21.589	30.764	16.234
24	245.430	189.040	202.444	212.305	29.460
48	358.829	323.036	321.963	334.609	20.982
72	420.138	393.948	379.922	398.003	20.412
96	435.580	418.582	401.711	418.624	16.935
124	435.805	432.793	415.518	428.039	10.947
144	444.518	443.853	441.285	443.219	1.707
168	442.115	451.107	436.680	443.301	7.286

Based on the permeation results of Example 8, listed in Table 8B, the following flux results listed in Table 8C below were obtained:

TABLE 8C

μg/cm²/hr					
Hours	**Test 8-1**	**Test 8-2**	**Test 8-3**	**Average of three tests**	**Std Dev**
6	8.251	3.533	3.598	5.127	2.706
24	10.226	7.877	8.435	8.846	1.227
48	7.476	6.730	6.708	6.971	0.437
72	5.835	5.472	5.277	5.528	0.284
96	4.537	4.360	4.184	4.361	0.176
124	3.515	3.490	3.351	3.452	0.088
144	3.087	3.082	3.064	3.078	0.012
168	2.632	2.685	2.599	2.639	0.043
$F_{6\text{-}96}$	**4.069**	**4.317**	**4.037**	**4.141**	**0.154**
CORR	**0.920**	**0.945**	**0.930**	**0.932**	**0.013**

EXAMPLE 9

A active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 9A below:

TABLE 9A

Ingredient	Amount (gm)
Loratadine	0.24
Ethyl Acetate	1.78
BIO PSA 7-4302 (adhesive solution) containing 11.63 silicone adhesive (60 % solids)	19.38
Total	21.4

The formulation of Table 9A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3.

The formulation of Example 9A was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (9-1, 9-2, and 9-3) were conducted giving the results listed in Table 9B below:

TABLE 9B

	$\mu g/cm^2$				
Hours	Test 9-1	Test 9-2	Test 9-3	Average of three tests	Std Dev
6	70.513	52.306	34.329	52.383	18.092
24	325.937	331.333	293.360	316.877	20.544
48	639.013	547.878	503.103	563.331	69.260
72	809.531	697.645	650.643	719.273	81.622
96	856.208	750.846	704.606	770.553	77.699
124	892.737	784.874	746.189	807.933	75.947
144	928.925	836.425	766.745	844.032	81.357
168	919.161	849.990	812.193	860.448	54.245

Based on the permeation results of Example 9, listed in Table 9B, the following flux results listed in Table 9C below were obtained:

TABLE 9C

μg/cm²/hr					
Hours	Test 9-1	Test 9-2	Test 9-3	Average of three tests	Std Dev
6	11.752	8.718	5.722	8.730	3.015
24	13.581	13.806	12.223	13.203	0.856
48	13.313	11.414	10.481	11.736	1.443
72	11.243	9.690	9.037	9.990	1.134
96	8.919	7.821	7.340	8.027	0.809
124	7.199	6.330	6.018	6.516	0.612
144	6.451	5.809	5.325	5.861	0.565
168	5.471	5.059	4.834	5.122	0.323
F_{6-96}	**8.921**	**7.631**	**7.353**	**7.968**	**0.836**
CORR	**0.962**	**0.959**	**0.962**	**0.961**	**0.002**

EXAMPLE 10

A active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 10A below:

TABLE 10A

Ingredient	Amount (gm)
Loratadine	0.36
Ethyl Acetate	2.67
BIO PSA 7-4302 (adhesive solution) containing 11.96 gm silicone adhesive (60 % solids)	19.93
Total	22.96

The formulation of Table 10A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3.

The formulation of Example 10A was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (10-1, 10-2, and 10-3) were conducted giving the results listed in Table 10B below:

TABLE 10B

$\mu g/cm^2$					
Hours	**Test 10-1**	**Test 10-2**	**Test 10-3**	**Average of three tests**	**Std Dev**
6	103.382	105.542	89.338	99.421	8.798
24	385.736	387.593	348.592	374.094	21.793
48	637.848	659.757	591.666	629.757	34.759
72	832.501	854.233	769.620	818.785	43.942
96	897.573	954.671	857.260	903.168	48.946
124	972.628	1026.660	933.732	977.679	46.669
144	1041.228	1107.161	1003.008	1050.466	52.687
168	1051.728	1140.184	1036.631	1076.181	55.940

Based on the permeation results of Example 10, listed in Table 10B, the following flux results listed in Table 10C below were obtained:

TABLE 10C

$\mu g/cm^2/hr$					
Hours	**Test 10-1**	**Test 10-2**	**Test 10-3**	**Average of three tests**	**Std Dev**
6	17.230	17.590	14.890	16.570	1.466
24	16.072	16.150	14.540	15.587	0.908
48	13.289	13.745	12.326	13.120	0.724
72	11.563	11.864	10.689	11.372	0.610
96	9.350	9.944	8.930	9.408	0.510
124	7.844	8.280	7.530	7.884	0.376
144	7.231	7.689	6.965	7.295	0.366
168	6.260	6.787	6.170	6.406	0.333
F_{6-96}	**8.831**	**9.407**	**8.499**	**8.912**	**0.459**
CORR	**0.970**	**0.977**	**0.976**	**0.974**	**0.004**

EXAMPLE 11

A active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 11A below:

TABLE 11A

Ingredient	Amount (gm)
Loratadine	0.4
Ethyl Acetate	3.0
BIO PSA 7-4302 (adhesive solution) containing 17.6 gm silicone adhesive (60 % solids)	29.3
Transcutol P (solvent)	2.0
Total	34.7

The formulation of Table 11A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3 using Transcutol P as an additional solvent.

The formulation of Example 11A was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (11-1, 11-2, and 11-3) were conducted giving the results listed in Table 11B below:

TABLE 11B

			$\mu g/cm^2$		
Hours	**Test 11-1**	**Test 11-2**	**Test 11-3**	**Average of three tests**	**Std Dev**
6	133.990	155.952	140.876	143.606	11.233
24	515.838	553.145	539.020	536.001	18.836
30	555.286	591.475	589.167	578.643	20.260
48	683.414	725.466	718.901	709.260	22.623
54	695.520	751.848	742.940	730.103	30.279
72	783.265	845.732	833.738	820.912	33.150
78	782.751	837.382	845.070	821.734	33.979
99	868.499	913.301	877.658	886.486	23.670
120	918.598	970.121	944.529	944.416	25.762
144	946.115	1004.137	964.594	971.615	29.641
150	936.874	984.544	961.619	961.012	23.841
168	951.645	1006.483	993.268	983.799	28.619

Table 11C lists further data with respect to Test 11-3.

TABLE 11C

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm² (μg/cm²)
11-3	6	20.744	12	248.928	1	20.744	0.00	248.928	140.876
	24	77.642	12	931.704	1	77.642	20.744	952.448	539.020
	30	78.556	12	942.672	1	78.556	98.386	1041.058	589.167
	48	91.113	12	1093.356	1	91.113	176.942	1270.298	718.901
	54	87.060	12	1044.720	1	87.060	268.055	1312.775	742.940
	72	93.175	12	1118.100	1	93.175	355.115	1473.215	833.738
	78	87.079	12	1044.948	1	87.079	448.290	1493.238	845.070
	99	84.621	12	1015.452	1	84.621	535.369	1550.821	877.658
	120	87.416	12	1048.992	1	87.416	619.990	1668.982	944.529
	144	83.086	12	997.032	1	83.086	707.406	1704.438	964.594
	150	75.724	12	908.688	1	75.724	790.492	1699.180	961.619
	168	74.074	12	888.888	1	74.074	866.216	1755.104	993.268

Based on the permeation results of Example 11, listed in Table 11B, the averages of the permeation tests were calculated and the flux results listed in Table 11D below were obtained:

TABLE 11D

	μg/cm²/hr				
Hours	Test 11-1	Test 11-2	Test 11-3	Average of three tests	Std Dev
6	22.332	25.992	23.479	23.934	1.872
24	21.493	23.048	22.459	22.333	0.785
30	18.510	19.716	19.639	19.288	0.675
48	14.238	15.114	14.977	14.776	0.471
54	12.880	13.923	13.758	13.520	0.561
72	10.879	11.746	11.580	11.402	0.460
78	10.035	10.736	10.834	10.535	0.436
99	8.773	9.225	8.865	8.954	0.239
120	7.655	8.084	7.871	7.870	0.215
144	6.570	6.973	6.699	6.747	0.206
150	6.246	6.564	6.411	6.407	0.159
168	5.665	5.991	5.912	5.856	0.170
F_{6-99}	**6.851**	**7.164**	**7.071**	**7.029**	**0.161**
CORR	**0.914**	**0.913**	**0.902**	**0.910**	
F_{6-168}	**3.958**	**4.094**	**3.969**	**4.007**	**0.076**
CORR	**0.882**	**0.878**	**0.867**	**0.876**	

EXAMPLE 12

A active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 12A below:

TABLE 12A

Ingredient	Amount (gm)
Loratadine	0.4
Ethyl Acetate	3.0
BIO PSA 7-4302 (adhesive solution) containing 17.6 gm silicone adhesive (60 % solids)	29.3
Lauryl Acohol (solvent)	2.0
Total	34.7

The formulation of Table 12A was prepared and incorporated into a permeation testing apparatus according to the same procedure as in Example 3 using lauryl alcohol as an additional solvent.

The formulation of Example 12A was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (12-1, 12-2, and 12-3) were conducted giving the results listed in Table 12B below:

TABLE 12B

	$\mu g/cm^2$				
Hours	**Test 12-1**	**Test 12-2**	**Test 12-3**	**Average of three tests**	**Std Dev**
6	171.613	167.470	145.806	161.630	13.859
24	603.924	573.643	553.767	577.111	25.258
30	648.367	661.962	595.567	935.299	35.074
48	803.563	770.051	738.869	770.828	32.354
54	832.797	779.924	749.892	787.538	41.974
72	932.645	881.734	847.836	887.405	42.688
78	937.072	895.118	853.752	895.314	41.660
99	978.713	946.745	921.427	948.962	28.707
120	1019.499	994.321	969.105	994.308	25.197
144	1072.582	1013.288	1009.257	1031.709	35.454
150	1046.531	1027.470	989.674	1021.225	28.938
168	1064.410	1030.903	1035.502	1043.605	18.164

Table 12C lists further data with respect to Test 12-3.

TABLE 12C

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm² (μg/cm²)
12-3	6	21.470	12	257.640	1	21.470	0.000	257.640	145.806
	24	79.753	12	957.036	1	79.753	21.470	978.506	553.767
	30	79.262	12	951.144	1	79.262	101.223	1052.367	595.567
	48	93.758	12	1125.096	1	93.758	180.485	1305.581	738.869
	54	87.568	12	1050.816	1	87.568	274.243	1325.059	749.892
	72	94.693	12	1136.316	1	94.693	361.811	1498.127	847.836
	78	87.673	12	1052.076	1	87.673	456.504	1508.580	853.752
	99	90.332	12	1083.984	1	90.332	544.177	1628.161	921.427
	120	89.825	12	1077.900	1	89.825	634.509	1712.409	969.105
	144	88.252	12	1059.024	1	88.252	724.334	1783.358	1009.257
	150	78.014	12	936.168	1	78.014	812.586	1748.754	989.674
	168	78.261	12	939.132	1	78.261	890.600	1829.732	1035.502

Based on the permeation results of Example 12, listed in Table 12B, the averages of the permeation tests were calculated and the flux results listed in Table 12D below were obtained:

TABLE 12D

	μg/cm²/hr				
Hours	**Test 12-1**	**Test 12-2**	**Test 12-3**	**Average of three tests**	**Std Dev**
6	28.602	27.912	24.301	26.938	2.310
24	25.164	23.902	23.074	24.046	1.052
30	21.612	22.065	19.852	21.177	1.169
48	16.741	16.043	15.393	16.059	0.674
54	15.422	14.443	13.887	14.584	0.777
72	12.953	12.246	11.776	12.325	0.593
78	12.014	11.476	10.946	11.478	0.534
99	9.886	9.563	9.307	9.585	0.290
120	8.496	8.286	8.076	8.286	0.210
144	7.448	7.037	7.009	7.165	0.246
150	6.977	6.850	6.598	6.808	0.193
168	6.336	6.136	6.164	6.212	0.108
F_{6-99}	**7.791**	**7.344**	**7.339**	**7.492**	**0.260**
CORR	**0.905**	**0.902**	**0.912**	**0.906**	
F_{6-168}	**4.176**	**4.036**	**4.197**	**4.136**	**0.088**
CORR	**0.852**	**0.859**	**0.879**	**0.863**	

EXAMPLE 13

A Loratadine reservoir and active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 13A below:

TABLE 13A

Ingredient	*Amount (gm)*
Donor Solution	
Loratadine	0.35
Ethanol	22.0 (95%)
Water	27.0
Total	49.35
Membrane	Polyethylene
Active Drug/Adhesive Matrix	
Loratadine	0.12 gm
BIO PSA 7-4302 (adhesive solution) containing11.49 gm silicone adhesive (60% solids)	19.14 gm
Ethyl acetate solvent	0.89 gm
Total	20.15 gm

The formulation of Table 13A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Loratadine is dissolved with ethanol and water and the solution is placed into the donor cell.
2. Loratadine is dispersed in the adhesive solution and ethyl acetate solvent to form the active drug/adhesive matrix.
3. The polyethylene membrane is coated with active drug/adhesive matrix and placed against the donor cell and dried. The coated surface of the membrane is positioned opposite from the donor cell.
4. Thereafter, the human cadaver skin is placed between the coated membrane surface and the receptor cell and the apparatus is secured.

The formulation of Example 13 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (13-1, 13-2, and 13-3) were conducted giving the results listed in Table 13B below:

TABLE 13B

μg/cm²					
Hours	Test 13-1	Test 13-2	Test 13-3	Average of three tests	Std Dev
6	72.594	58.406	69.079	66.694	7.387
24	217.680	175.542	197.278	196.833	21.073
30	255.681	203.923	227.740	229.115	25.906
48	348.695	283.263	310.261	314.073	32.882
54	385.778	308.526	336.586	343.630	39.105
72	487.268	391.914	419.969	433.050	49.004
78	523.816	419.585	446.677	463.359	54.081
96	629.393	505.149	532.631	555.721	65.262
102	662.817	528.167	555.429	582.138	71.188
120	762.760	613.895	634.252	671.302	80.061
144	920.453	741.930	759.623	807.335	98.361
168	1068.287	865.187	872.726	935.400	115.145

Table 13C lists further data with respect to Test 13-3.

TABLE 13C

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm² (μg/cm²)
13-3	6	10.987	4	43.948	4	43.948	0.000	43.948	69.079
	24	20.390	4	81.560	4	81.560	43.948	125.508	197.278
	30	4.845	4	19.380	4	19.380	125.508	144.888	227.740
	48	13.125	4	42.500	4	52.500	144.888	197.388	310.261
	54	4.187	4	16.748	4	16.748	197.388	214.136	336.586
	72	13.262	4	53.048	4	53.048	214.136	267.184	419.969
	78	4.248	4	16.992	4	16.992	267.184	284.176	446.677
	96	13.671	4	54.684	4	54.684	284.176	338.860	532.631
	102	3.626	4	14.504	4	14.504	338.860	353.364	555.429
	120	13.014	4	52.056	4	52.056	353.364	405.420	637.252
	144	19.463	4	77.852	4	77.852	405.420	483.272	759.623
	168	17.989	4	71.956	4	71.956	483.272	555.228	872.726

Based on the permeation results of Example 13, listed in Table 13B, the averages of the permeation tests were calculated and the flux results listed in Table 13D below were obtained:

TABLE 13D

µg/cm²/hr					
Hours	**Test 13-1**	**Test 13-2**	**Test 13-3**	**Average of three tests**	**Std Dev**
6	12.099	9.735	11.513	11.116	1.231
24	9.070	7.314	8.220	8.201	0.878
30	8.523	6.797	7.591	7.637	0.864
48	7.264	5.901	6.464	6.543	0.685
54	7.144	5.713	6.233	6.364	0.724
72	6.768	5.443	5.833	6.015	0.681
78	6.716	5.379	5.727	5.941	0.693
96	6.556	5.262	5.548	5.789	0.680
102	6.498	5.178	5.445	5.707	0.698
120	6.356	5.116	5.310	5.594	0.667
144	6.392	5.152	5.275	5.606	0.683
168	6.359	5.150	5.195	5.568	0.685

EXAMPLE 14

A Loratadine reservoir and active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 14A below:

TABLE 14A

Ingredient	***Amount (gm)***
Donor Solution	
Loratadine	0.35
Ethanol	22.0 (95%)
Water	27.0
Total	49.35
Membrane	Polyethylene
Active Drug/Adhesive Matrix	
Loratadine	0.24 gm
BIO PSA 7-4302 (adhesive solution) containing11.63 gm silicone adhesive (60% solids)	19.38 gm
Ethyl acetate solvent	1.78 gm
Total	21.4 gm*

* Reflects removal of solvent from formulation upon drying

The formulation of Example 14 was prepared and incorporated into a permeation testing apparatus according to the procedure as in Example 13.

The formulation of Example 14 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three

permeation tests (14-1, 14-2, and 14-3) were conducted giving the results listed in Table 14B below:

TABLE 14B

	μg/cm²				
Hours	Test 14-1	Test 14-2	Test 14-3	Average of three tests	Std Dev
6	99.616	93.914	65.244	86.258	18.421
24	289.299	264.313	215.108	256.240	37.749
30	329.217	303.791	247.476	293.495	41.832
48	407.865	397.793	316.888	374.182	49.873
54	434.033	430.324	339.025	401.127	53.814
72	510.588	523.829	405.564	479.994	64.797
78	536.221	556.542	427.281	506.681	69.509
96	617.391	654.782	494.782	588.985	83.697
102	638.743	684.929	511.311	611.661	89.922
120	713.411	777.743	574.052	688.402	104.123
144	828.802	914.128	671.500	804.810	123.080
168	935.549	1041.830	761.138	912.839	141.717

Table 14C lists further data with respect to Test 14-3.

TABLE 14C

Test #	Sampling Time (Hours)	Drug Conc. (µg/ml)	Receptor Volume (ml)	Drug Amount (µg)	Sampling Volume (ml)	Drug Loss due to Sampling (µg)	Cumulative Drug Loss (µg)	Cumulative Amount Permeated (µg)	Amount Permeated per cm^2 (µg/cm^2)
14-3	6	10.377	4	41.508	4	41.508	0.000	41.508	65.244
	24	23.836	4	95.344	4	95.344	41.508	136.852	215.108
	30	5.148	4	20.592	4	20.592	136.852	157.444	247.476
	48	11.040	4	44.160	4	44.160	157.444	201.604	316.888
	54	3.521	4	14.084	4	14.084	201.604	215.688	339.025
	72	10.583	4	42.332	4	42.332	215.688	258.020	405.564
	78	3.454	4	13.816	4	13.816	258.020	271.836	427.281
	96	10.736	4	42.944	4	42.944	271.836	314.780	494.782
	102	2.629	4	10.516	4	10.516	314.780	325.296	511.311
	120	9.979	4	39.916	4	39.916	325.296	365.212	574.052
	144	15.499	4	61.996	4	61.996	365.212	427.208	671.500
	168	14.257	4	57.028	4	57.028	427.208	484.236	761.138

Based on the permeation results of Example 14, listed in Table 14B, the averages of the permeation tests were calculated and the flux results listed in Table 14D below were obtained:

TABLE 14D

	µg/cm^2/hr				
Hours	**Test 14-1**	**Test 14-2**	**Test 14-3**	**Average of three tests**	**Std Dev**
6	16.603	15.652	10.874	14.376	3.070
24	12.054	11.013	8.963	10.677	1.573
30	10.974	10.126	8.249	9.783	1.394
48	8.497	8.287	6.602	7.795	1.039
54	8.038	7.969	6.278	7.428	0.997
72	7.092	7.275	5.633	6.667	0.900
78	6.875	7.135	5.478	6.496	0.891
96	6.431	6.821	5.154	6.135	0.872
102	6.262	6.715	5.013	5.997	0.882
120	5.945	6.481	4.784	5.737	0.868
144	5.756	6.348	4.663	5.589	0.855
168	5.569	6.201	4.531	5.434	0.844
$F_{6\text{-}96}$	**5.283**	**5.906**	**4.439**	**5.209**	**0.736**
CORR	**0.979**	**0.992**	**0.983**		

EXAMPLE 15

A Loratadine reservoir and active drug/adhesive matrix formulation was prepared having the formulation set forth in Table 15A below:

TABLE 15A

Ingredient	*Amount (gm)*
Donor Solution	
Loratadine	0.17
Ethanol	10.93 (95%)
Water	13.4
Klucel HF (gelling agent/enhancer)	0.50
Total	25.0 gm
Membrane	Polyethylene
Active Drug/Adhesive Matrix	
Loratadine	0.12 gm
BIO PSA 7-4302 (adhesive solution) containing11.49 gm silicone adhesive (60% solids)	19.14 gm
Ethyl acetate solvent	0.89 gm
Total	20.15 gm

The formulation of Table 15A was prepared and incorporated into a permeation testing apparatus according to the following procedure:

1. Loratadine is dissolved with ethanol and water, Klucel HF is added and the solution is placed into the donor cell.
2. Loratadine is dispersed in the adhesive solution and ethyl acetate solvent to form the active drug/adhesive matrix.
3. The polyethylene membrane is coated with active drug/adhesive matrix and placed against the donor cell and dried. The coated surface of the membrane is positioned opposite from the donor cell.
4. Thereafter, the human cadaver skin is placed between the coated membrane surface and the receptor cell and the apparatus is secured.

The formulation of Example 15 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (15-1, 15-2, and 15-3) were conducted giving the results listed in Table 15B below:

TABLE 15B

µg/cm²					
Hours	**Test 15-1**	**Test 15-2**	**Test 15-3**	**Average of three tests**	**Std Dev**
6	30.400	31.356	33.475	31.744	1.574
24	113.504	96.723	104.500	104.909	8.398
30	138.050	114.351	120.220	124.207	12.342
48	220.527	176.029	183.955	193.504	23.736
54	245.590	194.380	203.129	214.366	27.392
72	336.788	265.985	281.761	294.845	37.171
78	359.116	286.556	303.001	316.224	38.044
96	450.921	350.096	383.057	394.691	51.410
120	591.832	455.829	507.498	518.386	68.652
144	685.488	556.102	631.384	624.325	64.981
168	780.272	635.766	730.428	715.489	73.402

Table 15C lists further data with respect to Test 15-3.

TABLE 15C

Test #	Sampling Time (Hours)	Drug Conc. (µg/ml)	Receptor Volume (ml)	Drug Amount (µg)	Sampling Volume (ml)	Drug Loss due to Sampling (µg)	Cumulative Drug Loss (µg)	Cumulative Amount Permeated (µg)	Amount Permeated per cm² (µg/cm²)
15-3	6	4.550	13	59.150	1	4.550	0.000	59.150	33.475
	24	13.854	13	180.102	1	13.854	4.550	184.652	104.500
	30	14.925	13	194.025	1	14.925	18.404	212.429	120.220
	48	22.440	13	291.720	1	22.440	33.329	325.049	183.955
	54	23.320	13	303.160	1	23.320	55.769	358.929	203.129
	72	32.214	13	418.782	1	32.214	79.089	497.871	281.761
	78	32.623	13	424.099	1	32.623	111.303	535.402	303.001
	96	40.995	13	532.935	1	40.995	143.926	676.861	383.057
	120	54.756	13	711.828	1	54.756	184.921	896.749	507.498
	144	67.383	13	875.979	1	67.383	239.677	1115.656	631.384
	168	75.622	13	983.606	1	75.662	307.060	1290.666	730.428

Based on the permeation results of Example 15, listed in Table 15B, the averages of the permeation tests were calculated and the flux results listed in Table 15D below were obtained:

TABLE 15D

$\mu g/cm^2/hr$					
Hours	**Test 15-1**	**Test 15-2**	**Test 15-3**	**Average of three tests**	**Std Dev**
6	5.067	5.226	5.579	5.291	0.262
24	4.729	4.030	4.354	4.371	0.350
30	4.602	3.812	4.007	4.140	0.411
48	4.594	3.667	3.832	4.031	0.495
54	4.548	3.600	3.762	3.970	0.507
72	4.678	3.694	3.913	4.095	0.516
78	4.604	3.674	3.885	4.054	0.488
96	4.697	3.647	3.990	4.111	0.536
120	4.932	3.799	4.229	4.320	0.572
144	4.760	3.862	4.385	4.336	0.451
168	4.644	3.784	4.348	4.259	0.437
F_{6-96}	**4.651**	**3.544**	**3.830**	**4.008**	**0.575**
CORR	**1.000**	**1.000**	**0.998**		

EXAMPLE 16

A Loratadine reservoir and active drug/adhesive matrix formulation was prepared having the formulation of Table 16A below:

TABLE 16A

Ingredient	*Amount (gm)*
Donor Solution	
Loratadine	0.17
Ethanol	10.93 (95%)
Water	13.4
Klucel HF (gelling agent/enhancer)	0.50
Total	25.0 gm
Membrane	Polyethylene
Active Drug/Adhesive Matrix	
Loratadine	0.24 gm
BIO PSA 7-4302 (adhesive solution) containing11.63 gm silicone adhesive (60% solids)	19.38 gm
Ethyl acetate solvent	1.78 gm
Total	21.4 gm

The formulation of Example 16 was prepared and incorporated into a permeation testing apparatus according to the procedure as in Example 15.

The formulation of Example 16 was tested using a permeation cell with a definable surface area for permeation. The receptor of the permeation cell was Ethanol:water (40:60). Three permeation tests (16-1, 16-2, and 16-3) were conducted giving the results listed in Table 16B below:

TABLE 16B

	μg/cm²				
Hours	Test 16-1	Test 16-2	Test 16-3	Average of three tests	Std Dev
6	36.962	56.230	36.616	43.269	11.226
24	123.022	152.233	110.046	128.434	21.608
30	144.736	172.600	126.108	147.815	23.398
48	219.344	253.782	185.170	219.432	34.306
54	248.951	275.052	203.915	242.639	35.986
72	341.293	369.066	266.361	325.573	53.126
78	367.063	390.341	275.970	344.458	60.444
96	469.268	481.973	342.796	431.346	76.949
120	624.439	618.731	449.999	564.390	99.106
144	748.033	737.652	533.364	673.016	121.054
168	854.492	842.808	607.081	768.127	139.592

Table 16C lists further data with respect to Test 16-3.

TABLE 16C

Test #	Sampling Time (Hours)	Drug Conc. (μg/ml)	Receptor Volume (ml)	Drug Amount (μg)	Sampling Volume (ml)	Drug Loss due to Sampling (μg)	Cumulative Drug Loss (μg)	Cumulative Amount Permeated (μg)	Amount Permeated per cm² (μg/cm²)
16-3	6	4.977	13	64.701	1	4.977	0.000	64.701	36.616
	24	14.575	13	189.475	1	14.575	4.977	194.452	110.046
	30	15.637	13	203.281	1	15.637	19.552	222.833	126.108
	48	22.462	13	292.006	1	22.462	35.189	327.195	185.170
	54	23.282	13	302.666	1	23.282	57.651	360.317	203.915
	72	29.979	13	389.727	1	29.979	80.933	470.660	266.361
	78	28.979	13	376.727	1	28.979	110.912	487.639	275.970
	96	35.833	13	465.829	1	35.833	139.891	605.720	342.796
	120	47.648	13	619.424	1	47.648	175.724	795.148	449.999
	144	55.314	13	719.082	1	55.314	223.372	942.454	533.364
	168	61.079	13	794.027	1	61.079	278.686	1072.713	607.081

Based on the permeation results of Example 16, listed in Table 16B, the averages of the permeation tests were calculated and the flux results listed in Table 16D below were obtained:

TABLE 16D

	µg/cm²/hr				
Hours	**Test 16-1**	**Test 16-2**	**Test 16-3**	**Average of three tests**	**Std Dev**
6	6.160	9.372	6.103	7.212	1.871
24	5.126	6.343	4.585	5.351	0.900
30	4.825	5.753	4.204	4.927	0.780
48	4.570	5.287	3.858	4.572	0.715
54	4.610	5.094	3.776	4.493	0.666
72	4.740	5.126	3.699	4.522	0.738
78	4.706	5.004	3.583	4.416	0.775
96	4.888	5.021	3.571	4.493	0.802
120	5.204	5.156	3.750	4.703	0.826
144	5.195	5.123	3.704	4.674	0.841
168	5.086	5.017	3.614	4.572	0.831
$F_{6\text{-}96}$	**4.722**	**4.647**	**3.318**	**4.229**	**0.790**
CORR	**0.998**	**0.999**	**0.999**		

In vitro skin permeation studies with cadaver skin quantitatively predict the pharmacokinetics and extent of drug absorption from the transdermal delivery dosage form. Matching in vitro skin donors to the in vivo population improves the correlation. Further improvements in this correlation are achieved by matching application sites.

It will be readily apparent that various modifications to the invention may be made by those skilled in the art without departing from the scope of this invention. For example, many different transdermal delivery systems may be utilized in order to obtain the relative release rates and plasma levels described herein. Further, it is possible that mean values for plasma concentrations over a particular patient population for a particular described time point along the dosing interval may vary from the plasma concentration ranges described herein for that time point. Such obvious modifications are considered to be within the scope of the appended claims.